REMARKS

Status of the Claims

Claims 24-27, 29-36, 38, 40, 42, and 44 are canceled, without prejudice or disclaimer, and claim 28 is currently amended. No new matter has been added. Upon entry of this Amendment, claims 1, 6-7, 9-10, 14, 16-17, 19-23, 28, 37, 39, 41, 43, and 45 are pending, and elected claims 28, 37, 39, 41, 43, and 45 should be examined. Applicants will request rejoinder of claims 1, 6-7, 9-10, 14, 16-17, and 19-23 with the elected claims when the elected claims are allowed.

Rejections- 35 U.S.C. § 101

Claims 24-33 and 36-45 were rejected under 35 U.S.C. § 101 for allegedly lacking a specific, substantial, and credible utility, or alternatively, a well-established utility. Final Office Action of January 29, 2004, page 3. These same rejections were maintained in the Advisory Action of August 10, 2004. Applicants respectfully traverse this rejection.

In the Response filed July 28, 2004, Applicants indicated that "HEMBA1004850 expression correlates with protein glycosylation, a complication associated with diabetes. Moreover, the specification discloses 'vascular endothelial cells are affected with glycated proteins present in blood.' See specification, page 407, lines 24-25." Yet the PTO alleged that these arguments are unpersuasive on the grounds that "the specification appears to only have 284 pages." Advisory Action, page 2.

The as-filed application contains a specification (2742 pages), claims (81 pages), abstract (1 page) and a Sequence Listing (13,211 pages). The complete application was submitted to the PTO in 6 boxes. See attached copy of the itemized PTO date-stamped return post card of July 28, 2000 (enclosed for consideration). Accordingly, Applicants respectfully request that the Examiner consider the complete specification. In an effort to assist the Examiner, Applicants direct the Examiner to specification pages 407, 420, and 632, a copy of each page from applicants' file is attached herewith (enclosed). The examiner is respectfully requested to recheck the file for its complete contents.

As described in the specification, SEQ ID NO: 706 and SEQ ID NO: 6223 of the elected claims have a specific utility, i.e., a utility specific to SEQ ID NO: 706 and SEQ ID NO: 6223. Both SEQ ID NO: 706 and SEQ ID NO: 6223 are described as associated with diabetes. Specifically, according to the specification, the expression level of HEMBA1004850, a clone containing SEQ ID NO: 706 and SEQ ID NO: 6223, was elevated in endothelial cells in a glycated protein specific manner (see p. 420, lines 30-42, and p. 632, line 9 of Table 169). As further disclosed in the specification on page 407, line 21, a non-enzymatic protein glycation reaction is believed to cause of a variety of chronic diabetic complications. Schmidt AM et al., *J Clin Invest.* Sep. 96(3):1395-403 (1995) (reporting a gene whose expression is significantly elevated or decreased in a glycated protein-specific manner in an endothelial cell and is associated with a diabetic complication caused by a glycated protein) (previously submitted for consideration). HEMBA1004850 contains such a gene and both SEQ ID NO: 706 and SEQ ID NO: 6223. Therefore, the specification states that both SEQ ID NO: 706 and SEQ ID NO: 6223 find a specific and credible utility in the diagnosis and treatment of diabetes.

Contrary to the PTO's position, the as-filed specification not only discloses that HEMBA1004850 is associated with diabetes, but the specification also indicates that elevated HEMBA1004850 expression was observed in human pulmonary arterial cells cultured in medium containing glycosylated bovine serum albumin or an advanced glycosylated end product thereof, compared with control bovine serum albumin. Accordingly, HEMBA1004850 expression correlates with protein glycosylation, a complication associated with diabetes. Moreover, the specification discloses "vascular endothelial cells are affected with glycated proteins present in blood." See specification, page 407, lines 24-25. Clearly, it is useful to determine whether or not vascular endothelial cells have been exposed to glycated proteins. Since HEMBA1004850 expression increases when endothelial cells are exposed to glycated proteins, HEMBA1004850 provides a useful diagnostic marker for assaying cell exposure to such glycated proteins.

Applying the standards of MPEP § 2107.01, the present invention finds a substantial,

i.e., "real world," use, because it provides a means for determining (e.g., assaying) whether or not vascular endothelial cells have been exposed to glycated proteins, a useful thing to know. That is, since HEMBA1004850 expression level is elevated when endothelial cells are contacted with glycated proteins, HEMBA1004850 is a useful diagnostic marker for indicating exposure of cells to such glycated proteins.

As the present invention finds a specific, substantial, and credible utility, or alternatively, a well-established utility, the rejection is improper and should be withdrawn.

Rejections- 35 U.S.C. § 112, first paragraph (Enablement)

Claims 24-33 and 36-45 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. In short, the PTO asserted that the claimed invention is not supported by a specific, substantial, and credible utility or a well-established utility, and therefore one skilled in the art would not know how to use the claimed invention. Final Office Action, page 7. Applicants respectfully traverse this rejection.

As previously discussed, the subject matter embraced by the elected claims and sequences find specific, substantial, and credible utility. This issue has been addressed in the previous section and need not be repeated here. In light of the disclosed utility, however, Applicants respectfully submit that one skilled in the art, guided by the present specification's teachings, would readily know how to make and use the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections- 35 U.S.C. § 112, first paragraph (written description)

There are two sets of rejections, each of which is addressed under separate headers.

A. Claims 28, 34-35, 37, 39, 41, 43, and 55 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. Claim 28, and its dependent claims 34-35, 37, 39, 41, 43, and 45, are rejected on the grounds that the language "secretory or membrane protein associated with diabetes" allegedly does not find support in the as-filed specification. Final Office Action, page 8. As the present version of the claims avoids this issue, the

rejection should be withdrawn.

B. Claims 24-33 and 36-45 were rejected on the grounds that the claims "encompass fragments and oligonucleotide (claims 24, 25, 34) as well as recited percentages of identity (claim 28) and hybridization to sequences (claim 28) which do not meet the written description provision of 35 U.S.C. § 112, first paragraph." Final Office Action, pages 8-10. As there are 12 grounds for rejection, each one is addressed as enumerated below.

1. Claims 24 and 34 were rejected for reciting "fragment of the nucleotide sequence." Final Office Action, page 9. As claims 24 and 34 are canceled without prejudice or disclaimer, the rejection should be withdrawn.

2. Claim 26 was rejected for reciting "the primer set." Final Office Action, page 9. As claim 26 is canceled without prejudice or disclaimer, the rejection should be withdrawn.

3. Claim 27 was rejected for reciting "the coding region of the polynucleotide." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

4. Claim 28 was rejected for reciting "comprising a coding region of the nucleotide sequence." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

5. Claim 28 was rejected for reciting "comprising a nucleotide sequence encoding a protein comprising the amino acid sequence." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

6. Claim 28 was rejected for reciting "the amino acid sequences." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

7. Claim 28 was rejected for reciting "up to 5 % of the amino acids are substituted, deleted, inserted, and/or added." Final Office Action, page 9. As the present version of the

claim avoids this issue, the rejection should be withdrawn.

8. Claim 28 was rejected for reciting "the nucleotide sequence." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

9. Claim 28 was rejected for reciting "comprises a nucleotide sequence encoding a protein comprising a secretory or membrane protein associated with diabetes." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

10. Claims 35-39 and 42-43 were rejected for reciting "the polynucleotide." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

11. Claims 40-41 and 44-45 were rejected for reciting "the vector." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

12. Claim 28 was rejected for reciting "95 % identity." Final Office Action, page 9. As the present version of the claim avoids this issue, the rejection should be withdrawn.

Accordingly, Applicants respectfully request reconsideration and withdrawal of each rejection.

Rejections- 35 U.S.C. § 112, second paragraph

Claims 28, 34, 37, 39, and 43 were rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. Specifically, the PTO maintains that the phrase "associated with diabetes" is allegedly unclear. Final Office Action, page 11. The present version of the claims avoids this issue. Accordingly, the rejection should be withdrawn.

Rejections-35 U.S.C. § 102(e)

Claims 28, 34-35, 37, 39, 41, 43, and 45 were rejected under 35 U.S.C. § 102(e)(2) as allegedly anticipated by Shin et al. (USPN 6,291,645). Specifically, the PTO alleged that "claim 28 does not specify if the coding region is an entire coding region or not." Advisory Action, page 2. As the present version of the claims avoid this issue, the rejection should be withdrawn.

CONCLUSION

As the above-presented amendments and remarks address and avoid each rejection presented by the Examiner, withdrawal of each rejection and allowance of each claim is respectfully requested. No new matter has been added.

If there are any questions concerning this application, the Examiner is courteously invited to contact the undersigned counsel.

Respectfully submitted,

Date 09-28-2004

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicants hereby petition for any needed extension of time.

Enclosures: PTO date-stamped postcard 07-28-2000; and
As-filed U.S. application No. 09/629,469, pages 407, 420, and 632.

Docket No. 084335/0123

Receipt is hereby acknowledged of the following:

Applicants: Toshio Ota et al.
Serial No.: To be assigned
Filing Date: July 28, 2000
For: PRIMERS FOR SYNTHESIZING FULL-LENGTH cDNA AND THEIR USE

1. Utility Patent Application Transmittal, including 2742 pages specification; 81 pages claims; 1 page abstract; 3 sheets informal drawings; and 13211 pages Sequence Listing. **APPLICATION CONSISTS OF 6 BOXES**

Date Due: July 28, 2000
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(a)

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MAMMA1002428, MAMMA1002590, MAMMA1001186, MAMMA1002267, MAMMA1002322, MAMMA1001956, MAMMA1002155, NT2RP4000210, MAMMA1002622, NT2RP3004125, MAMMA1001220, MAMMA1001683, NT2RP3004348, Y79AA1000214, Y79AA1000833, NT2RP4000212, MAMMA1002230, MAMMA1001452, MAMMA1001620, MAMMA1001256, MAMMA1001760, NT2RP3004349, MAMMA1001783, MAMMA1001907, MAMMA1002009, MAMMA1002545, NT2RP4000214, NT2RP4000728, MAMMA1001465, MAMMA1001154, MAMMA1001198, MAMMA1001343, MAMMA1002310, NT2RP4000035, NT2RP4000833, MAMMA1003150, MAMMA1002886, NT2RP4001938, NT2RM2000260, MAMMA1002629, MAMMA1002973, MAMMA1002721, MAMMA1002909, NT2RP4001100, NT2RM1000857, NT2RP4000878, MAMMA1002844, NT2RM1000039, NT2RP4001174, MAMMA1002665, MAMMA1003047, NT2RM1000086, NT2RM1000260, NT2RM1000355, MAMMA1002701, NT2RP4000918, MAMMA1002830, MAMMA1002970, NT2RP4001677, NT2RM2000422, MAMMA1003004, MAMMA1002673, MAMMA1003031, MAMMA1002764, MAMMA1002858, NT2RP4001679, NT2RP4002888, MAMMA1002711, NT2RP4001276, NT2RM1000018, NT2RP4001568, NT2RM1000883.

Thus, characteristic features in the expression of a gene are illustrated by comparing and statistically analyzing the expression of many genes.

Analysis of disease-associated genes

Non-enzymic protein glycation reaction is believed to be a cause of a variety of chronic diabetic complications. Accordingly, genes of which expression is elevated or decreased in a glycated protein-specific manner in the endothelial cells are associated with diabetic complications caused by glycated proteins. Vascular endothelial cells are affected with glycated proteins present in blood. Reaction products of non-enzymic protein glycation include amadori compound (glycated protein) as a mildly glycated protein and advanced glycation endproduct as a heavily glycated protein. Hence, a survey was carried out for genes of which expression levels are varied depending on the presence of these glycated proteins in endothelial cells. The mRNAs were extracted from endothelial cells that were cultured in the presence or absence of glycated protein. The mRNAs were converted into radiolabeled first strand cDNAs for preparing probes. The probes were hybridized to the above-mentioned DNA array. Signal of each DNA spot was detected by BAS2000 and analyzed by ArrayGauge (Fuji Photo Film Co., Ltd.).

Advanced glycation endproduct of bovine serum albumin was prepared as follows: bovine serum albumin (BSA; Sigma) was incubated in a phosphate buffer solution containing 50 mM glucose at 37°C for 8 weeks; and the resulting brownish BSA was dialyzed against a phosphate buffer solution.

Human normal pulmonary arterial endothelial cells (Cell Applications) were cultured in an Endothelial Cell Growth Medium (Cell Applications). The culture dish (Farcon) with the cells were incubated in a CO_2 incubator (37°C, 5% CO_2, in a humid atmosphere). When the cells were grown to be confluent in the dish, 250 μ g/ml of bovine serum albumin (sigma), glycated bovine serum albumin (Sigma) or advanced glycation endproduct of bovine serum albumin was added thereto and the cells were incubated for 33 hours. The mRNA was extracted from the cells by using a FastTack$^{(TM)}$ 2.0 kit (Invitrogen). The labeling of hybridization probe was carried out by using the mRNA according to the same procedure as described above.

Table 169 shows the expression level of each cDNA in human pulmonary arterial endothelial cells cultured in a medium containing bovine serum albumin (sigma), glycated bovine serum albumin (Sigma) or advanced glycation endproduct of bovine serum albumin. Genes of which expression was detected in the endothelial cell are as follows:

Y79AA1000850, Y79AA1000966, Y79AA1000968, Y79AA1000985, Y79AA1001061,
Y79AA1001068, Y79AA1001077, Y79AA1001078, Y79AA1001105, Y79AA1001145,
Y79AA1001211, Y79AA1001216, Y79AA1001228, Y79AA1001236, Y79AA1001299,
Y79AA1001394, Y79AA1001402, Y79AA1001511, Y79AA1001533, Y79AA1001548,
Y79AA1001555, Y79AA1001581, Y79AA1001585, Y79AA1001603, Y79AA1001647,
Y79AA1001665, Y79AA1001679, Y79AA1001711, Y79AA1001805, Y79AA1001827,
Y79AA1001846, Y79AA1001866, Y79AA1001875, Y79AA1001923, Y79AA1001963,
Y79AA1002089, Y79AA1002093, Y79AA1002115, Y79AA1002125, Y79AA1002209,
Y79AA1002211, Y79AA1002220, Y79AA1002246, Y79AA1002258, Y79AA1002311,
Y79AA1002351, Y79AA1002361, Y79AA1002472, Y79AA1002482

Signal ratios of EC_AGE_BSA to EC_BSA and of EC_glycated_BSA to EC_BSA were calculated for each gene. Genes with high signal ratios were selected. In the case of calculating the ratio of signal value of 40 or less to that of more than 40, such signal values were, for convenience, taken as 40 instead of the real values. When the ratio EC_AGE_BSA/EC_BSA is 2 or more, expression of the genes exhibiting such ratio is expected to be elevated due to advanced glycation endproduct of bovine serum albumin. The higher the value is, the higher the gene expression level is. When the ratio EC_AGE_BSA/EC_BSA ranges from 0.5 to 2, expression of the genes exhibiting such ratio is expected to be unaffected due to advanced glycation endproduct of bovine serum albumin. When the ratio EC_AGE_BSA/EC_BSA is less than 0.5, expression of the genes exhibiting such ratio value is expected to be decreased due to advanced glycation endproduct of bovine serum albumin. The lower the value is, the lower the gene expression level is.

Clone with EC_AGE_BSA/EC_BSA ratio of 2 or higher are as follows: HEMBA1003958, MAMMA1001256, PLACE2000411.

Clone with EC_AGE_BSA/EC_BSA ratio of 0.5 or less is as follows: MAMMA1001783.

These cDNAs are associated with diabetes.

When the ratio EC_glycated_BSA/EC_BSA is 2 or more, the expression level of the gene exhibiting such ratio is expected to be elevated due to glycated bovine serum albumin. The higher the value is, the higher the gene expression level is. When the ratio EC_glycated_BSA/EC_BSA ranges from 0.5 to 2, the expression level of the gene exhibiting such ratio is expected to be unaffected with glycated bovine serum albumin. When the ratio EC_glycated_BSA/EC_BSA is less than 0.5, the expression level of a gene exhibiting such ratio is expected to be decreased due to glycated bovine serum albumin. The lower the value is, the lower the gene expression level is.

Clones with EC_glycated_BSA/EC_BSA ratio of 2 or more are as follows: HEMBA1004850, MAMMA1001256, MAMMA1002132 and PLACE3000119.

A clone with EC_glycated_BSA/EC_BSA ratio of 0.5 or less is as follows: MAMMA1001783.

These cDNAs are also associated with diabetes.

Analysis of genes associated with neural cell differentiation

Genes involved in neural cell differentiation are useful for treating neurological diseases. It is possible that genes with varying expression levels in response to induction of cellular differentiation in neural cells are associated with neurological diseases.

A survey was performed for genes of which expression levels are varied in response to induction of differentiation (stimulation by retinoic acid (RA)) in cultured cells of a neural strain, NT2.

	HEMBA1004797	69.02	75.8	68.09	1.1	0.99
	HEMBA1004803	139.28	172.03	148.1	1.24	1.06
	HEMBA1004806	20.24	18.76	19.51	1	1
	HEMBA1004807	25.93	24.81	28.08	1	1
5	HEMBA1004816	66.84	72.32	80.51	1.08	1.2
	HEMBA1004820	20.72	27.49	22.78	1	1
	HEMBA1004833	58.77	77.82	68.76	1.32	1.17
	HEMBA1004847	55.11	54.09	68.09	0.98	1.24
	HEMBA1004850	41.24	94.77	74.52	2.3	1.81
10	HEMBA1004863	17.09	30.6	32.89	1	1
	HEMBA1004864	47.54	48.72	67.61	1.02	1.42
	HEMBA1004865	37.45	42.36	43.32	1.06	1.08
	HEMBA1004880	67.85	83.27	79.43	1.23	1.17
	HEMBA1004882	55.71	59.71	71.5	1.07	1.28
15	HEMBA1004885	5.26	5.42	10.69	1	1
	HEMBA1004889	39.97	53.79	59.53	1.34	1.49
	HEMBA1004900	24.64	37.16	35.42	1	1
	HEMBA1004909	37.38	55.77	52.81	1.39	1.32
	HEMBA1004918	52.56	69.3	75.53	1.32	1.44
20	HEMBA1004923	66.42	56.65	57.91	0.85	0.87
	HEMBA1004929	14.53	20.24	16.08	1	1
	HEMBA1004930	64.2	73.28	84.98	1.14	1.32
	HEMBA1004933	25.53	28.37	38.67	1	1
	HEMBA1004934	34.74	34.56	31.42	1	1
25	HEMBA1004937	30.99	32.44	39.53	1	1
	HEMBA1004943	26.88	32.39	33.5	1	1
	HEMBA1004944	47.48	54.15	57.28	1.14	1.21
	HEMBA1004946	110.22	99.09	106.8	0.9	0.97
	HEMBA1004952	18.65	22.44	23.74	1	1
30	HEMBA1004954	51.59	56.66	59.07	1.1	1.14
	HEMBA1004956	24.4	30.29	25.59	1	1
	HEMBA1004960	50.95	69.7	77.84	1.37	1.53
	HEMBA1004971	147.9	185.55	169.84	1.25	1.15
	HEMBA1004972	25.23	21.63	24.54	1	1
35	HEMBA1004973	29.7	24.12	26.9	1	1
	HEMBA1004977	68.37	56.37	65.48	0.82	0.96
	HEMBA1004978	87.36	98.52	102.09	1.13	1.17
	HEMBA1004980	64.46	65.18	58.56	1.01	0.91
	HEMBA1004982	19.91	18.27	24.85	1	1
40	HEMBA1004983	48.65	57.05	55.03	1.17	1.13
	HEMBA1004995	54.11	50.11	50.53	0.93	0.93
	HEMBA1005004	35.78	37.22	37.94	1	1
	HEMBA1005008	56.93	57.2	46.58	1	0.82
	HEMBA1005009	60.37	59.99	53.66	0.99	0.89
45	HEMBA1005019	52.03	55.66	59.82	1.07	1.15
	HEMBA1005021	75.62	83.62	95.86	1.11	1.27